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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,753	PIZZA, MARIAGRAZIA	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,8,10,12,14-19,22-26 and 28* is/are pending in the application.

4a) Of the above claim(s) *15-19,22-25 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 6, 8, 10, 12, 14, and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/27/2009 has been entered.

The amendment, filed 3/27/2009, and remarks, filed 12/30/2008, are acknowledged. Claims 4, 6, 8, 10, 12, and 14 are amended. Claims 5, 7, 9, 11, and 13 are cancelled. Claims 4, 6, 8, 10, 12, 14-19, 22-26, and 28 are pending. Claims 15-19, 22-25, and 28 are withdrawn as being drawn to non-elected inventions. Claims 4, 6, 8, 10, 12, 14, and 26 are currently under examination.

Claim Rejections Withdrawn

The rejection of claims 4-14 and 26 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the five meningococcal antigens consisting of the sequences of SEQ ID NO:2, 3, 4, 5, and 6, does not reasonably provide enablement for the full breadth of the instant claims, is withdrawn in lieu of the rejection set forth below.

The rejection of claims 4-14 and 26 under 35 U.S.C. 103(a) as being unpatentable over Fraser *et al.* (WO 99/57280, 1999) in view of Comanducci *et al.* (J. Exp. Med., 195:1445-1454, 6/2002, IDS filed 4/8/2005), is withdrawn for the following reasons.

As set forth below, the only enabled composition encompassed by the claims is a composition containing the proteins comprising the sequences of SEQ ID NO:2, 7 and 8. As shown in Giuliani *et al.* this combination of fusion polypeptides and NadA induced immune responses that were generally more potent than those induced by the individual antigens (see Table 1 and page 10835, column 2). Therefore, this composition provided unexpected results.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 4, 6, 8, 10, 12, 14, and 26 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That the specification provides a good summary of the five antigens claimed. Applicant asserts that NadA has been described including alignments showing conserved regions, expression of variants, and states that fragments have been explored. Applicant states that many allelic variants of NMB1870 have been disclosed and states that the specification cites two sources, one of which provides 22 sequences and the other of which disclosed 23 sequences.

2. That *Falkner v. Inglis* is relevant to the instant case. Applicant asserts that the court upheld claims as enabled and meeting the written description requirement even though the specification did not disclose a single working embodiment within the scope of the claims and did not disclose the sequence of any poxvirus. Applicant asserts that the claims in *Falkner* cover all possible poxviruses and argues that the number of permutations of this genome alone is far greater than the number encompassed by the instant claims. Applicant argues that merely calculating a large number is not sufficient for establishing that the written description requirements have not been met, given the decision in *Falkner*.

Applicant asserts that they have demonstrated that the five antigens work together to provide protection across a wide ranges of strains and one of skill in the art would infer that these antigens must have epitopes that are in common across a significant fraction of the strains. Applicant suggests that, because of this, one of skill in the art would accept that variants of these proteins should have the same epitopes and therefore be capable of providing the claimed protection. Applicant compares the instant case to *Falkner*, stating that the present claims are directed to five proteins and variants from a single species while *Falkner* covered an entire family of viruses without providing a single example of a variant that worked.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, applicant is reminded that the claims are not simply drawn to the five antigens named. The claims are drawn to compositions that elicit a specific type of antibody response against specific organisms. While the specification and the art have described variants of the proteins listed in the claims, out of the unlimited number of possible polypeptides encompassed by the claims, the specification and the art have disclosed exactly one composition that is capable of eliciting a bactericidal antibody response against A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. The specification describes a composition containing three proteins: a fusion of NMB2132 and NMB1030, a fusion of NMB2091 and NMB1870, and NadA with

amino acids 351-405 deleted. All of these proteins had leader sequences removed from them. This is the only composition that has been shown to elicit the proper response. While other variants are known, none of them have been shown to elicit the response required by the claims; therefore simple disclosure of variants does not equate to disclosure of the variants required by the claims. Furthermore, the specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions, and/or deletions that may be made to the proteins listed. As a result, the possibilities are limitless and the members of the genus have no common structural attributes that identify the members of the genus.

Regarding argument 2, *Falkner v. Inglis* is only tangentially related to the instant situation and provides no support whatsoever of applicant's position. In *Falkner* as in the instant case, the sheer number of possibilities is not the issue. In *Falkner* the claims required inactivation of an essential gene. The court found that the essential genes for poxviruses were well-known in the art. This is why *Falkner* is different from the instant case. In *Falkner*, it was known what needed to be altered to achieve the claimed vaccine. In the instant case, it is completely unpredictable what changes can be made to the unlimited proteins encompassed and still have the required function. It is simply not the number of possibilities that is the issue; it is the complete lack of correlation between structure and function that creates the issue.

Applicant asserts that they have demonstrated that the five antigens work together to provide protection across a wide ranges of strains; however, this is not actually the case. Applicant has only demonstrated that the particular combination of two specific fusion proteins and a specific deletion mutant of NadA work together to provide protection across a wide ranges of strains. Applicants themselves have argued the results of the specific combination of fusion proteins and NadA are unexpected. The art shows that the results of amino acid changes on the immune response are completely unpredictable and even Giuliani *et al.* support this, showing that NadA did not perform well when fused to other proteins. This is exactly as one would expect considering how conformational changes alter antibody binding. Thus, fusing proteins together or altering their amino acid sequence in any way alters the immune response generated. Applicant has also asserted that one of skill in the art would infer that these antigens must have epitopes that are in common across a significant fraction of the strains. This is correct. However, neither applicant nor the art has described these epitopes.

As outlined previously, the rejected claims are drawn to compositions comprising five meningococcal antigens, wherein the composition is able to induce a bactericidal antibody response against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. Dependent claims limit the composition to where an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein, or variants thereof. In addition, there are claims drawn which list the "NadA" protein as SEQ ID NO:2; the "NMB1870" protein as SEQ ID NO:3; the "NMB2091" protein as SEQ ID NO:4; the "NMB1030" protein as SEQ ID NO:5; and the "NMB2132" protein as SEQ ID NO:6.

The claims are drawn to an unlimited genus of immunogenic compositions comprising polypeptides that are capable of inducing a bactericidal antibody response against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention. To adequately describe the genus of immunogenic compositions comprising the claimed composition, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*, not just those determinants that would elicit an immune response to the said polypeptides since a given polypeptide can be immunogenic but not induce a bactericidal antibody response directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*.

The specification discloses a composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3). This composition satisfies the written description requirements. Applicant has not demonstrated that any other composition, including variants of the above composition, is capable

of inducing a bactericidal antibody response directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*. The specification further does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic compositions to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (i.e. eliciting the recited immune response), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of immunogenic compositions that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical*

Co. Ltd., 18 USPQ2d 1016.

Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus"; accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically.

As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their

proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing an immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding. While the proteins in the claimed composition are known, neither applicant, nor the art have shown which portions of the proteins can be altered while still maintaining the necessary epitopes to induce a bactericidal antibody response. In addition, the written description requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*.

Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of immunogenic compositions that elicit the induction of bactericidal antibodies directed against two or more strains of hypervirulent lineages A4, ET-5, and lineage 3 strains of serogroup B *N. meningitidis*..

Absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change

or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement.

Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of immunogenic compositions to which the claims refer. Hence, none of the claims meet the written description requirements.

Additionally, claim 4 recites the designations "NadA" protein, "NMB1870" protein, "NMB2091" protein, "NMB1030" protein, and "NMB2132" protein. These terms constitute laboratory designations that do not convey any structural or functional limitations, and which are not described in the specification. Therefore, the proteins to which these designations refer have not been adequately described under the requirements of 35 USC 112, first paragraph. Consequently, only a composition containing the proteins comprising the sequences of SEQ ID NO:2, 7 and 8 satisfies the written description requirements of 35 USC 112, first paragraph.

New Claim Rejections

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6, 8, 10, 12, 14, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the proteins with the sequences of NO:2, 7 and 8, does not reasonably provide enablement for the full breadth of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments from the previous rejection (that are applicable) are addressed below.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to compositions comprising five meningococcal antigens: an "NadA" protein, a "NMB1870" protein, a "NMB2091" protein, a "NMB1030" protein, and a "NMB2132" protein, or variants thereof, wherein the composition is able to induce a bactericidal antibody response against hypervirulent lineages A4, ET-5, and lineage 3 of *N. meningitidis* serogroup B. In addition, there are claims drawn which list the "NadA" protein as SEQ ID NO:2; the "NMB1870" protein as SEQ ID NO:3; the "NMB2091" protein as SEQ ID NO:4; the "NMB1030" protein as SEQ ID NO:5; and the "NMB2132" protein as SEQ ID NO:6.

Breadth of the claims: The broadest claim encompasses an unlimited genus of any polypeptides capable of inducing the required immune response in any animal using any means of administration or adjuvant.

Guidance of the specification/The existence of working examples: The specification discloses a working example wherein a composition comprising an NadA polypeptide with the sequence of SEQ ID NO:2, a fusion protein with the sequence of SEQ ID NO:7 (a fusion of SEQ ID NOs 6 and 5), and a fusion protein with the sequence of SEQ ID NO:8 (a fusion of SEQ ID NO:4 and 3) is capable of inducing the required immune response. However, the specification does not disclose any other compositions (or variants of the above composition) that are capable of inducing the required bactericidal antibody response.

State of the art: While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al.* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie *et al.* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (Nature Biotechnology, 7:936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes

that can elicit a particular immune response to a given pathogen can only be identified empirically. As taught in basic immunology texts, an epitope or antigenic determinant interacts with its corresponding antibody based on the three-dimensional structure of both molecules and the fit between them (Cruse *et al.*, Illustrated Dict. of Immunology, 2nd ed., CRC Press, 2003, page 46). These epitopes can be conformational (or discontinuous) epitopes which are formed from separate regions in the primary sequence that are brought together by proper protein folding. Antibodies which bind to conformational epitopes will only bind to proteins folded into their proper native state (Cruse *et al.*, page 166). There are also linear epitopes, which are regions of six amino acids in the primary sequence of a protein. These are generally not found on the surface of a folded protein and are only available to antibodies upon denaturation of a protein (Cruse *et al.*, page 382). Since the instant claims involve methods of inducing an immune response specific for an organism, not antibodies specific for a particular linear protein, said antibodies must bind to a protein that is in the proper folded state and which is found on the surface of the organism, and therefore must bind to a conformational epitope. Since a conformational epitope is only found in a properly folded protein and can contain discontinuous portions of the protein, there is no way that one could determine whether a given polypeptide would bind to the antibody unless this were empirically tested. Any change (including deletions and substitutions), anywhere along the polypeptide is likely to alter the three-dimensional structure and folding of the protein, thus altering the antibody-antigen interaction. This is further supported by other authors such as McGuinness *et al.* (Mol. Microbiol., 7:505-514, 1993) and Moudallal *et al.* (EMBO Journal, 1:1005-1010, 1982), who have shown that amino acid deletions, even outside an epitope will alter protein conformation and change antibody-antigen binding. Applicant has asserted (backed by the 1990 Wells reference, which does not mention antigen-antibody binding) that the results of changes in the proteins of the invention are predictable. However, Blythe *et al.* (Protein Sci., 14:246-248, 2005) definitively state that one cannot reliably predict the location of epitopes. The sum of the art (both old and new) shows that with regard to generating a particular antibody response, the effects of alterations in the sequence of proteins is entirely unpredictable.

Consequently, in view of the lack of support in the art and specification, it would require undue experimentation on the part of the skilled artisan to make and use the composition as

claimed; therefore, the full scope of the claims is not enabled.

Applicant argues:

1. That one of skill in the art would have no difficulty making and using the compositions within the scope of the claims. Applicant asserts that one of skill in the art would infer that these antigens must have epitopes that are in common across a significant fraction of the strains; thus, one of skill in the art would accept that variants of these proteins should have the same epitopes and therefore be capable of providing the claimed protection.

2. That, because *Falkner* covered poxviruses that are unsequenced, it should not matter that the claims cover variants that could be obtained from strains that have not been sequenced. Applicant asserts that the disclosed proteins would allow one to readily recognize newly sequenced proteins from other strains and that cloning and sequencing these would be a trivial matter.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the quantity of experimentation needed is one of the factors involved in determining whether undue experimentation is required. In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. The instant claims encompass an unlimited number of polypeptide variants and there is absolutely no guidance whatsoever with regard to which portions of the proteins are required for the claimed function. The claimed composition must induce a bactericidal antibody response. This requires the generation of mutants, administration to animals to generate a response, and then further testing to determine whether the response was in fact a bactericidal antibody response. If every single person on the earth were somehow able to test 1 million compositions per hour for 24 hours a day, seven days a week, it would take $1x10^{248}$ years to test the compositions encompassed by the claims. Therefore, contrary to applicant's assertion, one of skill in the art would have a great deal of difficulty making and using the compositions within the scope of the claims. Applicant correctly states that these antigens must have epitopes that are in common across a significant fraction of the strains; however, both the art and the specification are

completely silent on the subject of what these epitopes are. Furthermore, it is well known that alterations in an amino acid sequence can affect antibody binding even when the alteration is far removed from the epitope.

Regarding argument 2, *Falkner v. Inglis* is only tangentially related to the instant situation and provides no support whatsoever of applicant's position. In *Falkner* as in the instant case, the sheer number of possibilities is not the issue. In *Falkner* the claims required inactivation of an essential gene. The court found that the essential genes for poxviruses were well-known in the art. This is why *Falkner* is different from the instant case. In *Falkner*, it was known what needed to be altered to achieve the claimed vaccine. In the instant case, it is completely unpredictable what changes can be made to the unlimited proteins encompassed and still have the required function. It is simply not the number of possibilities that is the issue; it is the complete lack of information regarding what changes can be made while maintaining the required function. Furthermore, applicants themselves have argued that the properties exhibited by the claimed composition are unexpected. On page 8 of the remarks, applicant states, "antigens cannot be combined to predictably to[sic] improve the composition."

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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